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EXAMINER
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HILL, KEVIN KAI

ART UNIT	PAPER NUMBER
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1633

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/815,557	<b>Applicant(s)</b> ENGELHARDT ET AL.	
	<b>Examiner</b> KEVIN K. HILL	<b>Art Unit</b> 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1)  Responsive to communication(s) filed on 13 November 2008.
- 2a)  This action is **FINAL**.                      2b)  This action is non-final.
- 3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4)  Claim(s) 2,4,6 and 8-57 is/are pending in the application.  
4a) Of the above claim(s) 8-12,14,17-19,21,22 and 24-53 is/are withdrawn from consideration.
- 5)  Claim(s) \_\_\_\_\_ is/are allowed.
- 6)  Claim(s) 2,4,6,13,15,16,20,23 and 54-57 is/are rejected.
- 7)  Claim(s) \_\_\_\_\_ is/are objected to.
- 8)  Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9)  The specification is objected to by the Examiner.
- 10)  The drawing(s) filed on \_\_\_\_\_ is/are: a)  accepted or b)  objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11)  The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12)  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a)  All    b)  Some \*    c)  None of:
1.  Certified copies of the priority documents have been received.
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>November 13, 2008</u> . | 6) <input type="checkbox"/> Other: _____  |

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**Detailed Action**  
***Election/Restrictions***

Applicant has elected with traverse the invention of Group I, claims 1-13 and 15-32, drawn to a method of identifying one or more agents with therapeutic activity to treat one or more symptoms of a disease which is associate with aberrant expression or activity of epithelial sodium channels (ENaC),

Within Group I, Applicant has further elected the restricted subgroup "IA", Claims 1-9, 13, 15-23 and 28-32, drawn to a method of identifying an agent with dual therapeutic activity in mammalian cells.

Within Group IA, Applicant has elected the following species:

- i) the physiological agent category, antibiotic, as recited in Claim 16,
- ii) the physiological agent compound, doxil, as recited in Claim 20. Upon further examination of the subject matter, the Examiner has extended the species to include doxorubicin.
- iii) the cellular functionality, wherein the agent modulates transcription of a molecule that regulates ENaC transcription, as recited in Claim 23,
- iv) the virus type, adeno-associated virus, as recited in Claim 4,
- v) the selected transcriptional agent activity, wherein the agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 7, and
- vi) the mammalian cell type species, human, as recited in Claim 15.

***Amendments***

Applicant's response and amendments, filed November 13, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 1, 3, 5 and 7, withdrawn Claims 8-12, 14, 17-19, 21-22 and 24-53, amended Claims 2, 4, 13, 15-16, 20 and 23, and added new claims, Claims 54-57.

Claims 8-12, 14, 17-19, 21-22 and 24-53 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 2, 4, 6, 13, 15-16, 20, 23 and 54-57 are under consideration.

***Examiner's Note***

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the November 13, 2008 response will be addressed to the extent that they apply to current rejection(s).

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### ***Priority***

Applicant's claim for the benefit of a prior-filed application parent provisional applications 60/459,323, filed March 31, 2003 and 60/512,347, filed October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

### ***Information Disclosure Statement***

Applicant has filed Information Disclosure Statements on November 13, 2008. The Examiner was able to consider these to the extent of time allowable. The signed and initialed PTO Forms 1449 are mailed with this action.

### ***Claim Objections***

1. **The prior objection to Claim 2 is withdrawn** in light of Applicant's amendments to the claims.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 2, 4, 6, 13, 15-16, 20 and 23 stand, and Claims 54-57 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the office action mailed August 13, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed November 13, 2008.

With respect to claim 2, and claims dependent thereon, the claimed invention is directed to a method to identify one or more agents with dual therapeutic activity, the method comprising the step of selecting one or more agents which enhances the transduction of a viral gene therapy vector, wherein said agent that enhances the transduction of a viral gene therapy vector also possesses the functional property of decreasing or increasing [modulating], directly or indirectly, the level or amount of transcription of one or more subunits of ENaC.

At issue for the purpose of written description requirements is the lack of written description for those agents possessing the required functional properties and those mammalian

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cells having aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC.

*Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

In analyzing whether the written description requirement is met for agent genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, doxorubicin is the only species whose complete structure is disclosed to possess the functional property of inhibiting the expression of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of the ENaC  $\gamma$ -subunit. The specification discloses that doxorubicin increases the CpG methylation of the  $\gamma$ -ENaC gene promoter (pg 15, Figure 11; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity through increases in  $\alpha$ - or  $\beta$ -ENaC subunit promoter CpG methylation (pg 96, line 19), as required by claim 23.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that agent may be, but is not limited to, those agents that inhibit transcription of one or more ENaC subunit genes, alter the level, amount or activity of a molecule that alters ENaC transcription, alter ENaC RNA stability, and/or alter the trafficking and processing of molecules, for instance, molecules of non-viral origin through intracellular compartments, including without limitation proteasomes, endosomes, and trans-Golgi, and/or through the cytosol, e.g., via cytoskeletal components such as microtubules or microfilaments. In one embodiment, the agent is not an antagonist of ENaC. In another embodiment, the agent is not an agent that binds a cell membrane bound protein, e.g. ENaC or the receptor for hepatocyte growth factor. In yet another embodiment, the agent is not an agent that alters post-translational processing of ENaC. In another embodiment, the agent is not a gene of, or a gene product encoded by, a mammalian genome, e.g., a protein encoded by a mammalian cell, the complement of the gene, or a portion of the gene or its complement, e.g., an antisense oligonucleotide (pg 4, lines 12-27).

However, the specification does not disclose any identifying characteristic as to how an artisan would have identified and differentiated one structurally and functionally distinct compound that possesses any one of such properties from another compound that might possess

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such properties. It is noted that all these agents vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

In analyzing whether the written description requirement is met for the genus of mammalian cells having increased expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, it is first determined whether a representative number of species have been described by their complete structure.

However, neither the specification nor the art teach the objective, quantitative values to determine whether the expression or activity of the  $\alpha$ ,  $\beta$  and  $\gamma$  ENaC subunits is increased in the enormous genus of mammalian cell types embraced by the claims. Regulation of ENaC activity can occur at different levels, i.e. transcription, translation, translocation and degradation, as well as single-channel open probability and conductance. ENaC subunits [ $\alpha$ ,  $\beta$  and  $\gamma$ ] have been shown to be transcriptionally up-regulated by aldosterone, a low sodium diet or dexamethasone in the kidney, colon and lung, in a tissue- and subunit-specific fashion (Audige et al, *Clinical Sci.* 104:389-395, 2003; pg. 390, col. 1, ¶2). Using quantitative, real-time polymerase chain reaction (QT-PCR), Audige et al sought to establish whether ENaC is transcriptionally regulated in nephrotic syndrome, and whether expression of ENaC subunit mRNAs and/or protein expression correlates with the profile of urinary sodium excretion using the experimental model of PAN-induced nephrotic syndrome in the rat. Audige et al found that mRNA levels of the  $\alpha$ ,  $\beta$  and  $\gamma$  ENaC subunits fluctuated over the course of the experiment, first increasing, then decreasing, having escaped regulation by aldosterone, and that the changes in mRNA levels are not paralleled by the amount of ENaC subunit protein expression, e.g. the abundance of  $\beta$ ENaC or  $\gamma$ ENaC protein did not significantly change throughout the study (pg 393, col. 2, Protein Expression and Discussion). Although significant sodium retention occurred from days 5 to 7 in the presence of high plasma aldosterone concentrations, ENaC mRNAs normalized and protein levels of ENaC subunits remained unchanged (pg 394, col. 1, ¶1).

Similarly, Bubien et al (*J. Biol. Chem.* 276(11): 8557-8566, 2001) teach that when comparing human lymphocytes from Liddle's disease patients and non-Liddle's disease patients, the Liddle's disease lymphocytes were 2.5 times more fluorescent than non-Liddle's cells when stained for expression of ENaC (pg 8562, col. 1, Immunohistochemical Analysis). However, the authors were unable to ascertain if the increased fluorescence was due to an increase in the amount of ENaC expressed on the cell surface or an increase in the number of exposed epitopes, because the exact number of epitopes and stoichiometry is not known. Bubien et al were unable to provide quantitative values of mRNA or protein expression of the  $\alpha$ ,  $\beta$  and  $\gamma$  ENaC subunits. ENaC is expressed in the kidney, colon, lung, retina and salivary gland.

The expression of ENaC subunits along the respiratory epithelium is complex and varies between species (Kellenberger et al, *Physiological Review* 82:735-767, 2002; pg 739, col. 1, Lungs). However, sodium channels, neither known nor contemplated by Applicant yet embraced by the claims, are still being identified in the art and thus the objective states of activity and how such genes are regulated is simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). Even within the contemplated ENaC

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$\alpha$ ,  $\beta$  and  $\gamma$  genes, the breadth of aberrant expression or activity of these genes is not fully described in the art because the art has not identified quantitative measurements to objectively determine what is "aberrant", especially with respect to the enormous genus of mammalian cell types embraced by the claims.

While the claim recites that the increased ENaC activity is relative to corresponding cells with a wildtype CFTR, neither the claims nor the specification establish a nexus between expression levels of ENaC and wildtype CFTR. As discussed above, the art already recognizes considerable uncertainty regarding normal vs. aberrant ENaC expression levels. Neither the art nor the specification disclose a predictable correlation between ENaC and wildtype CFTR. Furthermore, the claims embrace an enormous range of expression levels of wildtype CFTR, e.g. poorly transcribed and/or poorly translated CFTR RNA molecules encoding wildtype CFTR protein. Thus, the reference cell type is not adequately described so as to clearly and objectively identify which cell possesses increased expression of ENaC.

One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, does not suffice to define the genus because it is only an indication of what the genus does, rather than what it is. See *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such species of the genus may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally thought to exist, in the absence of knowledge as to what that material consists of, is not a description of that entire material.

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v.*

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*Wells Elecs., Inc.*, 525 U.S. 55, 68, 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)\*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

The specification fails to disclose sufficient identifying characteristics such as complete structure, partial structure, physical and/or chemical properties, or functional characteristics when coupled with a known or disclosed correlation between function and structure. The art does not teach a recognized or predictable correlation between a compound's structure and its functional ability to inhibit the expression or activity of ENaC, enhance the transduction of a viral vector, decrease the level or amount of transcription of one or more ENaC subunits, and/or modulate the transcription of one or more molecules that regulates ENaC transcription. While the specification discloses a laundry list of structurally diverse, possible compounds and agents (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3), the specification fails to disclose a representative number of species which would lead one skilled in the art to conclude that the Applicant was in possession of the claimed inventive genera. Rather, the agent species specifically disclosed in practice of the claimed inventions are Z-LLL, LLnL and doxorubicin (e.g. pg 72, lines 7-20), wherein those of ordinary skill in the art would recognize that these few species do not adequately represent the enormous genus of structurally diverse compounds disclosed in the above-mentioned laundry list.

While the specification discloses means for screening compounds that inhibit expression or activity of ENaC or enhance viral transduction, the specification does not disclose a correlation between selective inhibitory or enhancing activity and the structure of a putative inhibitor or enhancer, nor information regarding what structural features would likely be associated with the desired functional properties. While one of ordinary skill in the art would conclude that the Applicant would have been in possession of methods for identifying compounds that inhibit the expression or activity of ENaC, enhance the transduction of a viral vector, decrease the level or amount of transcription of one or more ENaC subunits, and/or modulate the transcription of one or more molecules that regulates ENaC transcription, one of



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ordinary skill in the art would not conclude that the Applicant would have been in possession of the enormous genus of compounds having the desired activity at the time of filing so as to perform the instantly claimed methods requiring the use of compounds identified by the disclosed screening methods. The practice of the instantly claimed methods to identify compounds with dual activities requires the artisan to select *a priori* a desired structure possessing a desired function, and thus requires prior knowledge of the structures and properties of a compound that would predictably result in the desired activity. However, the number of structures encompassed by the claims is vast and their corresponding properties as per the requirements of the claims are unknown (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3).

Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of agents which inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, wherein the selected agent is effective to decrease, directly or indirectly, the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector. The one species of agent specifically disclosed, doxorubicin, is not representative of the genus because the genus is highly variant.

Accordingly, given that the specification does not teach what is the complete structure of the agent species of the exceptionally broadly-defined "agent" genus, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials, that is a genus of agents which inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription, to perform the necessary active steps and effect the claimed methods, at the time the application was filed.

Based on the Applicant's specification, the skilled artisan cannot envision what mammalian cell expressing amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC would fall within the metes and bounds of the claims for possessing "increased expression or activity". Accordingly, given that the specification does not disclose the objective, quantifiable levels by which expression or activity is considered "increased", this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials, that is a genus of mammalian cells having increased expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, to perform the necessary active steps and effect the claimed methods, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

### ***Response to Arguments***

Applicant argues that:

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a) agents that enhance viral transduction and methods to identify those agents are well known to the art, see for example, Duan et al, 2000);

b) it is the function of the agent that identifies it for selection, e.g. an agent that enhances transduction of a viral gene therapy vector in mammalian cells, and thus the class of agents to be screened is adequately described;

c) the cells to which increased ENaC activity is compared to a wildtype CFTR are *in vitro*, not *in vivo*; and

d) the Examiner has set forth an apparent contradiction by asserting that the claims and specification do not establish a nexus between ENaC expression and wildtype CFTR; whereas, the art teaches a reciprocal expression relationship between ENaC and CFTR.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a-b), the Examiner acknowledges that Duan et al teach different chemical reagents that enhance AAV transduction from the basolateral surface of polarized bronchial epithelia (pg 1575, Figure 2). However, the Examiner respectfully reminds Applicant that the different chemical compounds contemplated in the instant specification, as well as those taught by Duan et al are structurally diverse, sharing no common core structure necessary and sufficient to enhance an enormous genus of viral vectors such that the artisan would recognize *a priori* that a specific agent would possess the desired function. Furthermore, dependent claim requires that said agent also modulates transcription of one or more molecules that regulates ENaC transcription. Such is not adequately described for the artisan to recognize *a priori* that a specific agent would possess the desired function. The additional references (Ravot, Rieger and Kipps, and Dhanak) do not further demonstrate that the art recognized a correlation between the structure of a compound and the functional ability of said compound to enhance transduction of an enormous genus of viral vectors and modulate transcription of one or more molecules that regulates ENaC transcription.

With respect to c-d), the substantive issue is that the art does not recognize objective, quantitative values to determine whether the expression or activity of the  $\alpha$ ,  $\beta$  and  $\gamma$  ENaC subunits is increased in the enormous genus of mammalian cell types embraced by the claims, alone or as compared to a corresponding cell with wildtype CFTR. While the art recognizes a

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generally reciprocal expression relationship between CFTR and ENaC within the same cell, neither the instant specification nor the prior art teach a correlation **between different cell populations**. Furthermore, the art recognizes that the expression of ENaC subunits is complex, challenging to measure and varies between species. The regulation of ENaC expression and/or activity can occur at different levels, i.e. transcription, translation, translocation and degradation, mRNA levels of the  $\alpha$ ,  $\beta$  and  $\gamma$  ENaC subunits fluctuating over the course of the experiment, as well as single-channel open probability and conductance. While the scientific evidence was demonstrated via cells and tissue *in vivo*, Applicant has provided no evidence that transcription, translation, translocation and degradation, mRNA levels of the  $\alpha$ ,  $\beta$  and  $\gamma$  ENaC subunits are not unpredictable and do not fluctuate when cells are cultured *in vitro*, and the specification fails to disclose how to overcome said difficulties when comparing a plurality of biomolecules between a first and a second cell populations.

3. **Claims 2, 4, 6, 13, 15-16, 20 and 23 stand, and Claims 54-57 are newly rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the office action mailed August 13, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed November 13, 2008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the

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state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

### ***The Breadth of the Claims and The Nature of the Invention***

The breadth of the claims is exceptionally large for encompassing an enormous genus of agents that inhibit expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ -,  $\beta$ - and  $\gamma$ -subunits of ENaC and/or enhance the transduction of a viral gene therapy vector.

The specification does not define the term “mammal”, but discloses a preferred mammalian embodiment that is human (pg 4, lines 1-4). The art recognizes mammals to reasonably encompass some 5,500 species (including Humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007). The art also recognizes that the mammalian body consists of a large genus of distinctly different organs, e.g. heart, lung, brain, muscle, skin, liver, etc., and an even larger genus of distinctly different cell types. Thus, the claimed inventions reasonably embrace any mammalian cell type that endogenously possesses, or is transformed with a nucleic acid encoding (pg 4, lines 7-8), an epithelial sodium channel.

The claimed inventions are directed to methods for identifying one or more agents with dual therapeutic activity. At issue for the purpose of enablement requirement is the method step of selecting an agent identified only by its *a priori* ability to enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription. The specification fails to disclose the ability to predictably identify the enormous genus of structurally diverse agents possessing functionally diverse properties contemplated in the specification (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3) that would inhibit the expression of ENaC **and** enhance viral transduction.

### ***The Existence of Working Examples and The Amount of Direction Provided by the Inventor***

The method comprises the step of selecting one or more agents which inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhances the transduction of a viral gene therapy vector and/or modulates the transcription of one or molecules that regulates ENaC transcription.

The elected embodiment of the agent is an antibiotic, specifically doxorubicin. The specification discloses that doxorubicin enhances rAAV transduction and increases the CpG methylation of the  $\gamma$ -ENaC gene promoter (pg 15, Figure 11; pg 83, lines 3-4; pg 93, lines 7-30). It is noted that the specification discloses that it is not known if doxorubicin inhibits long-term ENaC activity through increases in  $\alpha$ - or  $\beta$ -ENaC subunit promoter CpG methylation (pg 96, line 19), as embraced by claim 1 and required by claim 23.

The specification fails to disclose the necessary guidance to the artisan for choosing *a priori* an agent that inhibits expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC other than doxorubicin, or for choosing *a priori* an agent that enhances the transduction of a viral gene therapy vector.

While the specification discloses that LLnL and Dox are capable of enhancing AAV transduction (Figure 3) and inhibiting transcription of ENaC using the combination of LLnL/Dox

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(Figure 10), the specification does not disclose other agents that enhance the transduction of a viral gene therapy vector **and** inhibit ENaC expression or activity. Furthermore, the specification fails to disclose a nexus between the structural properties of a compound and its corresponding functional properties. Thus, a first species within the one of the broadly disclosed genera, e.g. a proteasome inhibitor, does not predictably correlate and immediately lead the artisan to identify another species within another one of the broadly disclosed genera, e.g. a food additive.

### ***The State of the Prior Art***

While Duan et al teach a screening method to identify agents that enhance AAV transduction, for example, the prior art does not teach predictable methods to identify agents that, at any particular concentration, enhance AAV transduction **and** inhibit the expression or activity of ENaC. Nor does the prior art teach a common chemical structure possessing the functional property of enhancing AAV transduction **and** inhibiting the expression or activity of ENaC that would guide the artisan to select a plurality of structurally and functionally diverse genera to be likely compounds having the instantly claimed desired properties.

### ***The Level of One of Ordinary Skill and The Level of Predictability in the Art***

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, cell biology and virology. Therefore, the level of ordinary skill in this art is high.

### ***The Quantity of Any Necessary Experimentation to Make or Use the Invention***

Given the absence of definitions and the lack of disclosure, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a particular agent has the required inherent property of inhibiting expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, wherein the selected agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC and/or enhance transduction of a viral gene therapy vector, so as to perform the method steps as claimed.

The artisan must perform extensive screening of an enormous genus of compounds to identify an agent that possesses either one of the first select desired property. Of those agents possessing either one of the first select desired property, the artisan must then test whether or not it possesses all of the secondary recited limitations so as to determine whether or not it possesses dual activity. There is no guidance in the prior art or the specification that establishes predictable correlation between the structural and functional properties of a first compound and the structural and functional properties of second compound. Thus, each agent from the broadly disclosed laundry list must be identified by trial and error.

Similarly, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a mammalian cell possesses the inherent property aberrant expression or activity of amiloride-sensitive epithelial sodium channels (ENaC) having  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of ENaC, so as to perform the method steps as claimed.

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The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

### ***Response to Arguments***

Applicant argues that:

- a) Applicant is not required to prepare and test all embodiments of the invention;
- b) the ordinary artisan can practice the invention without undue experimentation;
- c) any mammalian cell with increased ENaC expression or activity may be employed in the inventive method;
- d) the nexus between doxorubicin and the other agents to be screened in the inventive method is that they are selected from agents that enhance viral transduction;
- e) the claims are directed to a screening method, and the agents to be screened have a first functional property, and the agents identified by the screen have a second, different functional property. The fact that the property of the agents to be screened in the assay, and the property to be identified, are not necessarily related to a particular chemical structure is irrelevant;
- f) the need, and methodologies required, to carry out extensive synthesis and screening programs to locate biomolecules with particular properties do not constitute undue experimentation, referring to the nature of monoclonal antibody technology (*Hvbridge Inc. v. Monoclonal Antibodies Inc.*, 23 1 U.S.P.Q. 8 1, 84 (Fed. Cir. 1986); the fact that a given claim may encompass a variety of agents is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (*Ex parte Forman*, 230 U.S.P.Q.2d 456 (Bd. App. 1986). Evidence that screening numerous compounds to detect the effect of the compound is within the skill of the art, is provided in the abstracts for Cheng et al. and Dhanak et al; and
- g) the structure of monoclonal antibodies secreted from a set of hybridomas obtained from fusions with cells exposed to the same immunogen, is quite likely to be different.

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Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), Applicant is respectfully reminded that the method requires the step of selecting an agent identified only by its *a priori* ability to enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription. While the specification discloses a laundry list of structurally diverse agents possessing functionally diverse properties (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3), the specification fails to disclose those agents that do, in fact, possess the necessary properties to modulate transcription of one or molecules that regulate ENaC transcription **and** enhance viral transduction. There is nothing in the specification that would lead one to recognize any specific compound would possess the functional property to enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription. The mere mention of the enormous genus of structurally distinct compounds in the laundry list is insufficient to put one skilled in the art in the possession of the claimed invention as is required to support a conclusion of enablement (see *Impax v. Aventis*, 496 F.Supp.2d 428, D. Del. 2007).

With respect to b and d-e), the specification fails to disclose essential features of the invention, specifically the agent(s) that possesses a first functional property to enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription. It is generally recognized in the art that biological compounds often react unpredictably under different circumstances (*Nationwide Chem. Corp. v. Wright*, 458 F. supp. 828, 839, 192 USPQ95, 105(M.D. Fla. 1976); Affd 584 F.2d 714, 200 USPQ257 (5th Cir. 1978); *In re Fischer*, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)). The relative skill of the artisan or the unpredictability of the pharmaceutical art is very high. Where the physiological activity [enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription] of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved" (See *In re Fischer*, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970))), the skilled artisan would not know how to

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extrapolate the activity of a first compound in an enormous laundry list of compounds sharing no common core structure to a second compound within said laundry list.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed step of selecting an agent from the enormous laundry list of agents, identified only by its *a priori* ability to enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription constitute such a "germ of an idea". Thus, in light of the instant specification failing to disclose those compounds that possess the essential feature(s) of the invention, and the unpredictability in the art to extrapolate the physiological activity of a first compound towards the activity of a second compound having a completely different chemical structure, the Examiner maintains the position that it would be considered undue experimentation for the artisan to select an agent identified only by its *a priori* ability to enhance the transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription.

With respect to c), the Examiner acknowledges the breadth of the mammalian cells that may be employed in the inventive method.

With respect to f-g), Applicant is respectfully reminded that those of ordinary skill in the art recognize that monoclonal antibodies [hybridomas] share a common structural and functional property, i.e. those portions of the heavy and light chains that create the backbone for the epitope recognition motif, as well as constant domains that assist in the proper assembly and dimerization of individual polypeptides. In contrast, the laundry list of broadly disclosed genera of the instant application (pg 5, line 20- pg 6, line 4; pg 9, line 11-pg 10, line 7; pg 27, line 19-pg 34, line 3) do not share a common structural and functional property, except for the presence of carbon atoms and electrons. Because of the absence of disclosure in the instant specification, Applicant is requiring the artisan to discover for themselves those compounds that enhance the



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transduction of a viral gene therapy vector and/or modulate the transcription of one or molecules that regulates ENaC transcription, from which the artisan must then screen to discover for themselves those agents that possess the additional functional property to inhibit ENaC expression or activity. The Examiner maintains the position that such requires undue experimentation.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. **The prior rejection of Claims 1, 4-5, 13, 15-16, 20 and 23 under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; \*of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; \*of record in IDS) **is withdrawn** in light of Applicant's cancellation of Claim 1.

5. **Claims 2, 4, 6, 13, 15-16, 20 and 23 stand, and Claims 54-57 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Duan et al (J. Clin. Invest. 105:1573-1587, 2000; \*of record) in view of Kiyomiya et al (Cancer Res. 61:2467-2471, 2001; \*of record in IDS) and Maitra et al (2001; \*of record in IDS).

Bruno et al (FEBS Letters 427:241-246, 1998), Patel et al, Mol. Pharmacol. 52(4):658-666, 1997), Russell et al (PNAS 92:5719-5723, 1995; \*of record in IDS) and Flotte (2002; \*of record in IDS) are provided by the Examiner as evidentiary references.

This rejection is maintained for reasons of record in the office action mailed August 13, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed November 13, 2008.

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***Determining the scope and contents of the prior art.***

Duan et al teach a screening method to identify one or more agents with dual activities, the method comprising contacting *in vitro* mammalian cells with one or more agents and a viral gene therapy vector (pg 1575, col. 1 and Figure 2, Effect of Different Chemical Reagents on AAV transduction), wherein viral gene therapy vector is an AAV vector comprising a marker gene (pg 1576, Figure 3), wherein the cells are human bronchial airway [lung] epithelial cells (pg 1574, col. 1, Methods), wherein the proteasome modulating agent, e.g. LLnL, enhanced rAAV transduction of mammalian lung epithelial cells. Based upon the result achieved by the proteasome modulating agent LLnL, Duan et al suggest that proteasome inhibitors increase AAV transduction (pg 1583, col. 2).

Duan et al do not teach the selection of the instantly elected agent embodiment that is doxorubicin. However, at the time of the invention, Kiyomiya et al taught adriamycin (a synonym for doxorubicin) is a proteasome protease inhibitor in the same genus of proteasome inhibitors discussed in Duan et al that enhance rAAV transduction (pg 2470, col. 1).

Neither Duan et al nor Kiyomiya et al teach the step of contacting *in vitro* mammalian cells having increased ENaC expression, wherein the mammalian cells do not express functional CFTR. However, at the time of the invention, Maitra et al taught the step of contacting *in vitro* mammalian cells expressing the  $\Delta F508$ -CFTR mutation, which results in improper folding and trafficking of the CFTR protein, leading to its degradation in the endoplasmic reticulum by the 26S proteasome machinery of the cell, with doxorubicin. Maitra et al teach that of the more than 850 individual CFTR mutations leading to the CF phenotype that have been described, the most important is  $\Delta F508$  (phenylalanine deletion at amino acid position 508), which is seen in 70% of all CF patients. However, importantly, if this mutant protein is folded and expressed in the membrane, it functions normally as a chloride channel. Moreover, it is estimated that restoration of functional CFTR expression to 10% of normal levels would be sufficient to ameliorate the symptoms of the disease *in vivo*. Thus, there is great interest in development of strategies that can enhance  $\Delta F508$ -CFTR cell surface expression, which may be clinically useful in treatment of CF patients (pg C1031). Doxorubicin significantly increased functional cell surface expression and activity of CFTR and  $\Delta F508$ -CFTR.

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, cell biology and virology. Therefore, the level of ordinary skill in this art is high.

Doxorubicin has long been recognized in the art to be an anthracycline, antibiotic and chemotherapeutic agent.

Those of ordinary skill in the art have long-recognized that recombinant adeno-associated viral vectors are useful as gene therapy vectors, and that cystic fibrosis patients are candidates for gene therapy (Flotte).

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Similarly, CFTR has been shown to regulate ENaC (prior art cited in specification pg 1, lines 21-23), and those of ordinary skill in the art have long-recognized that a reciprocal expression relationship between CFTR and ENaC, wherein over-expression of ENaC suppresses CFTR expression and in CF mutant cells, ENaC expression is increased (e.g. Tsang et al, Japanese J. Physiol. 51(4):539-542, 2001; pg 542, col. 1).

Furthermore, doxorubicin had long been recognized in the art to be a DNA-damaging agent (Patel et al), and DNA-damaging agents had long been recognized in the art to enhance AAV transduction in both stationary and dividing cells (Russell et al), wherein those of ordinary skill in the art optimized the concentration of the DNA-damaging agent so as to enhance viral transduction with less cytotoxicity, thereby improving prospects for gene therapy by AAV vectors (Russell et al, pg 5719, Abstract, Introduction; pg 5720, Figure 2; pg 5721, Figure 3). Furthermore, Bruno et al taught that doxorubicin was known in the art to broadly affect the transcriptional machinery, e.g. RNA Polymerase II, the major RNA polymerase responsible for transcribing genes whose RNAs will be translated into proteins, e.g. one or more subunits of ENaC, as well as impairing the function of several known genes at the transcriptional level (pg 245, col. 1, ¶1). The art had long-recognized doxorubicin to affect the cellular transcriptional machinery, and the instant claims do not recite the degree to which the level of transcription is to be modulated. In light of the art-recognized property that doxorubicin impairs the transcriptional machinery and is a DNA-damaging agent, one of ordinary skill in the art would reasonably expect doxorubicin to inhibit the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription when used at the appropriate concentration.

Thus, absent evidence to the contrary, it is routine for the artisan to vary the effective concentration of a given agent, e.g. a transcriptional inhibitor/DNA-damaging agent such as doxorubicin, so as to achieve the desired result in a desired cell type, e.g. enhance rAAV transduction and inhibit ENaC expression or activity, when used at the optimized concentration.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute the proteasome inhibitor agent LLnL as taught by Duan et al with the proteasome inhibitor agent doxorubicin as taught by Kiyomiya et al in a screening method to identify one or more agents with dual activities with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. At the time of the invention, doxorubicin was recognized as another species within the genus of proteasome inhibitors **and** DNA-damaging agents recognized in the art to possess AAV transduction enhancement properties. An artisan would be motivated to substitute the proteasome inhibitor agent LLnL with the proteasome inhibitor agent doxorubicin in a screening method to identify one or more agents with dual activities because Duan et al suggest the investigation of additional agents to enhance AAV transduction (pg 1579, col. 1) and that the use of proteasome modulating agents to enhance AAV gene therapy vectors will provide new approaches for gene therapy of diseases such as cystic fibrosis (Abstract).

It also would have been obvious to one of ordinary skill in the art to substitute the human bronchial airway [lung] epithelial cells of Duan et al with mammalian cells having aberrant ENaC expression, wherein the mammalian cells do not express functional CFTR, as taught by

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Maitra et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute the human bronchial airway [lung] epithelial cells of Duan et al with mammalian cells having aberrant ENaC expression, wherein the mammalian cells do not express functional CFTR because Maitra et al teach that there is great interest in development of strategies that can enhance  $\Delta F508$ -CFTR cell surface expression, which may be clinically useful in treatment of CF patients (pg C1031), and that doxorubicin significantly increased functional cell surface expression and activity of CFTR and  $\Delta F508$ -CFTR.

It also would have been obvious to modify the method of Duan et al to comprise a step of assaying the mammalian cells that do not express functional CFTR for decreased or inhibited ENaC expression or activity with a reasonable expectation of success because those of ordinary skill in the art have long-recognized that a reciprocal expression relationship between CFTR and ENaC, and decreased or inhibited ENaC expression or activity would be an indicator of increased expression of functional CFTR, which would be of therapeutic value for those patients in need.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

### ***Response to Arguments***

Applicant argues that:

- a) Duan et al do not disclose a screening assay where agents that enhance viral transduction are screened for inhibition of ENaC activity or expression;
- b) there is nothing in Kiyomiya et al related to virus transduction or ENaC;
- c) there is nothing Maitra et al related to virus transduction or ENaC;
- d) Duan et al, Kiyomiya et al or Maitra et al, individually or in combination with each other, do not disclose or suggest contacting mammalian cells having increased expression or activity of ENaC with an agent that enhances viral gene therapy vector transduction and identifying one or more agents which also inhibit expression or activity of ENaC;
- e) the Examiner has not set forth a proper *prima facie* case of obviousness because the cited portions of Duan et al. and Kiyomiya et al., individually or in combination with each other, and the reasoning given above, do not provide the recited subject matter. For instance, Applicant is unable to find in Duan et al. and Kiyomiya et al., among other things, screening an agent that enhances viral transduction for inhibition of ENaC activity or expression. Applicant is unable to find in the Office Action a proper reason that remedies this deficiency;
- f) there is nothing in the cited art that provides a reasonable expectation that proteasome inhibitors other than LLnL or Z-LLL would alter AAV transduction;
- g) not all of the agents disclosed in Russell et al. appear to be "DNA damaging agents" nor enhanced AAV transduction; and
- h) the Examiner has not set forth a proper *prima facie* case of obviousness because the cited portions of Duan et al. and Maitra et al., individually or in combination with each other, and the reasoning given above, do not provide the recited subject matter. For instance, Applicant is unable to find in Duan et al., or Duan et al. and Maitra et al., among other things, screening an agent that enhances viral transduction for inhibition of ENaC activity or expression. Applicant is unable to find in the Office Action a proper reason that remedies this deficiency. Moreover, none

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of the cited art provides a reasonable expectation that an agent that enhances viral transduction, e.g., AAV transduction, may also inhibit ENaC expression or activity.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a-c), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to d-e and h), Applicant's phraseology [screening an agent that enhances viral transduction for inhibition of ENaC activity or expression] is but a re-statement of what is taught, suggested and/or motivated by the prior art, namely to find an agent that enhances the efficacy of a viral vector encoding CFTR to improve the therapeutic effect. However, the prior art recognized a reciprocal expression relationship between CFTR and ENaC (Tsang et al), and thus those of ordinary skill in the art would have appreciated that increased expression or activity of ENaC would naturally flow from the mammalian cells of Maitra et al having aberrant CFTR activity. The ordinary artisan would also have recognized that the addition of an agent that enhances AAV transduction (Duan et al, Kiyomiya et al) to improve the delivery of a therapeutic agent, e.g. a viral vector encoding a CFTR transgene to restore functional CFTR expression to at least 10% of normal levels, sufficient to ameliorate the symptoms of the disease (Maitra et al) would necessarily identify an agent which also inhibits expression or activity of ENaC, given the reciprocal expression relationship between CFTR and ENaC.

With respect to f-g), Russell et al demonstrate that it is routine for the artisan to screen other species within the same genus of a known first functional property [DNA-damaging agents] to ascertain if they share a second functional property [enhance AAV transduction]. While not all species may share both the first and the second functional properties, Russell et al demonstrate that the artisan has a reasonable expectation of success in finding those species which do share both the first and the second functional properties. In the instant case, doxorubicin was known in the prior art to: i) broadly affect the transcriptional machinery, e.g. RNA Polymerase II, the major RNA polymerase responsible for transcribing genes whose RNAs will be translated into proteins, e.g. one or more subunits of ENaC, as well as impairing the function of several known genes at the transcriptional level (Bruno et al), ii) be a DNA-damaging

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agent (Patel et al), wherein DNA-damaging agents had long been recognized in the art to enhance AAV transduction in both stationary and dividing cells (Russell et al), wherein those of ordinary skill in the art optimized the concentration of the DNA-damaging agent so as to enhance viral transduction with less cytotoxicity, thereby improving prospects for gene therapy by AAV vectors (Russell et al), and iii) be a proteasome protease inhibitor (Kiyomiya et al) in the same genus of proteasome inhibitors that enhance rAAV transduction (Duan et al). Thus, it is unclear how one of ordinary skill in the art would not have a reasonable expectation of success to think that doxorubicin would be capable of inhibiting the transcription or activity of one or more subunits of ENaC or one or molecules that regulate ENaC transcription when used at the appropriate concentration

### *Conclusion*

6. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

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If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

Examiner, Art Unit 1633

*/Q. JANICE LI, M.D./*

*Primary Examiner, Art Unit 1633*